Stem cell transplantation strategies for the restoration of cognitive dysfunction caused by cranial radiotherapy.

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Public Summary:
Radiotherapy often provides the only clinical recourse for those afflicted with primary or metastatic brain tumors. While beneficial, cranial irradiation can induce a progressive and debilitating decline in cognition that may, in part, be caused by the depletion of neural stem cells. Given the increased survival of patients diagnosed with brain cancer, quality of life in terms of cognitive health has become an increasing concern, especially in the absence of any satisfactory long-term treatments. To address this serious health concern we have used stem cell replacement as a strategy to combat radiation-induced cognitive decline. Our model utilizes athymic nude rats subjected to cranial irradiation. The ionizing radiation is delivered as either whole brain or as a highly focused beam. Two days following irradiation, human neural stem cells (hNSCs) were transplanted into the hippocampus. Rats were then assessed for changes in cognition, grafted cell survival and for the expression of differentiation-specific markers 1 and 4-months after irradiation. Our cognitive testing paradigms have demonstrated that animals engrafted with hNSCs exhibit significant improvements in cognitive function. Our data demonstrate direct cognitive benefits derived from engrafted human stem cells, suggesting that this procedure may one day afford a promising strategy for the long-term functional restoration of cognition in individuals subjected to cranial radiotherapy. To promote the dissemination of the critical procedures necessary to replicate and extend our studies, we have provided written and visual documentation of several key steps in our experimental plan, with an emphasis on stereotaxic radiosurgey and transplantation.

Scientific Abstract:
Radiotherapy often provides the only clinical recourse for those afflicted with primary or metastatic brain tumors. While beneficial, cranial irradiation can induce a progressive and debilitating decline in cognition that may, in part, be caused by the depletion of neural stem cells. Given the increased survival of patients diagnosed with brain cancer, quality of life in terms of cognitive health has become an increasing concern, especially in the absence of any satisfactory long-term treatments. To address this serious health concern we have used stem cell replacement as a strategy to combat radiation-induced cognitive decline. Our model utilizes athymic nude rats subjected to cranial irradiation. The ionizing radiation is delivered as either whole brain or as a highly focused beam to the hippocampus via linear accelerator (LINAC) based stereotaxic radiosurgery. Two days following irradiation, human neural stem cells (hNSCs) were stereotaxically transplanted into the hippocampus. Rats were then assessed for changes in cognition, grafted cell survival and for the expression of differentiation-specific markers 1 and 4-months after irradiation. Our cognitive testing paradigms have demonstrated that animals engrafted with hNSCs exhibit significant improvements in cognitive function. Unbiased stereology reveals significant survival (10-40%) of the engrafted cells at 1 and 4-months after transplantation, dependent on the amount and type of cells grafted. Engrafted cells migrate extensively, differentiate along glial and neuronal lineages, and express a range of immature and mature phenotypic markers. Our data demonstrate direct cognitive benefits derived from engrafted human stem cells, suggesting that this procedure may one day afford a promising strategy for the long-term functional restoration of cognition in individuals subjected to cranial radiotherapy. To promote the dissemination of the critical procedures necessary to replicate and extend our studies, we have provided written and visual documentation of several key steps in our experimental plan, with an emphasis on stereotaxic radiosurgey and transplantation.